

CH-8474  
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**METHOD FOR FORMING CC BONDS BETWEEN ELECTROPHILIC  
SUBSTRATES AND  $\pi$  COMPOUNDS IN NEUTRAL TO BASIC  
AQUEOUS OR ALCOHOLIC SOLVENTS WITHOUT THE USE OF A  
LEWIS OR PROTIC ACID**

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The invention relates to a method for forming carbon-carbon bonds by reacting electrophilic substrates with a solvolysis rate  $k_{EtOH}$  (25°C) of  $> 10^{-6} s^{-1}$  and  $\pi$  compounds, characterized in that the intermediate carbocations are generated in neutral to basic aqueous or alcoholic solvents or solvent mixtures without using a Lewis acid or protic acid.

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Lewis acid- (or else protic acid-) induced reactions of electrophiles such as, for example, alkyl halides with  $\pi$  compounds such as, for example, arenes or heteroarenes (Friedel-Crafts alkylations: C. Friedel, J.M. Crafts, J. Chem. Soc. 1877, 32, 725; C.C. Price, Org. React. 1946, 3, 1-82; G.A. Olah, Friedel-Crafts and Related Reactions, Wiley, New York, 1963-1964, Vol. 1 and 2; R. Taylor, Electrophilic Aromatic Substitution, Wiley, New York, 1990, pp. 187-203.), or other unsaturated systems represent important CC-linking reactions for introducing alkyl substituents into arenes or other  $\pi$  systems.

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In this method, which is frequently referred to as Friedel-Crafts, Hoaglin-Hirsch (R.I. Hoaglin, D.H. Hirsch, J. Am. Chem. Soc. 1949, 71, 3468-3472.), Hosomi-Sakurai (A. Hosomi, Acc. Chem. Res. 1988, 21, 200-206; I. Fleming, J. Dunogues, R. Smithers, The Electrophilic Substitution of Allylsilanes and Vinylsilanes, in: Organic Reactions, A. S. Kende (ed.), Wiley, New York, 1989, Vol. 37, 57-575.) or Mukaiyama reactions (T. Mukaiyama, M. Murakami, Synthesis 1987, 1043-1054; R. Mahrwald, Chem. Rev. 1999, 99, 1095-1120; M.T. Reetz, W.F. Maier, H. Heimbach, Chem. Ber. 1980, 113, 3734-3740; M.T. Reetz, W.F. Maier, I. Chatziiosifidis, A. Giannis, H. Heimbach, U. Löwe, Chem. Ber. 1980, 113, 3741-3757.), normally metal halides of the formula type  $MX_n$ , such as, for example,  $AlCl_3$ ,  $AlBr_3$ ,  $BCl_3$ ,  $BF_3$ ,  $FeCl_3$ ,  $TiCl_4$ ,  $SnCl_4$ ,  $SbF_5$ ,  $GaCl_3$ ,  $ZnCl_2$  (G.A. Olah, S. Kobayashi, M. Tashiro, J. Am. Chem. Soc. 1972, 94, 7448.) or  $POCl_3$  are employed to activate the electrophilic substrates and are irreversibly deactivated by hydrolysis in the working up of the reaction mixtures.

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The solvents frequently employed are chlorinated hydrocarbons which have a low coordination capacity for metal halides. Since the Lewis acids are moisture-sensitive, moisture is strictly excluded, causing the preparations to be very elaborate.

5 The use of aqueous reaction media has achieved great importance in synthetic organic chemistry. CC-linking reactions carried out in such solvents represent a great challenge in this connection (A. Lubineau, J. Ange, Y. Queneau, *Synthesis* 1994, 741-760; C.J. Li, *Chem. Rev.* 1993, 93, 2923-2035.). Furthermore, the reactivities and selectivities achieved in aqueous media are often better than under anhydrous conditions (S. Kobayashi, K. Manabe, *Chem. Eur. J.* 2002, 18, 4094-4101; S. Kobayashi, *Eur. J. Org.*  
10 *Chem.* 1999, 15-27.).

The range of application of Friedel-Crafts reactions is limited for a large number of reasons.

15 Many heteroaromatic compounds are unsuitable for Friedel-Crafts alkylation. In addition, numerous functional groups such as -OH, -OR, -NH<sub>2</sub>, -NR<sub>2</sub>, which are complexed by the Lewis acid, interfere with progress of the reaction (T. Laue, A. Plagens, *Namens- und Schlagwort-Reaktionen der organischen Chemie*, Teubner, Stuttgart, 1994, pp. 128-132.).

20 When alcohols are used as electrophiles, it is known in some cases that Lewis acids can be replaced by protic acids, in particular H<sub>2</sub>SO<sub>4</sub> or HF. However, considerable disadvantages arise in particular on use of HF. HF is highly toxic and corrosive.

Substrates which comprise acid-labile groups such as, for example, alkyl enol ethers, silyl enol ethers, ketene acetals or enamines may be decomposed by Lewis or protic  
25 acids.

The present invention is therefore based on the object of providing a method by which a carbon-carbon bond formation in the sense of a Friedel-Crafts or related reaction is brought about without the use of a Lewis or protic acid in nonchlorinated solvents and thus permits the use of a large number of additional substrates under moderate reaction  
30 conditions, providing conspicuous ecological and economic advantages compared with the established synthesis options.

This object is achieved by the use of compounds of the general formula type (I)



which have solvolysis rates of  $k_{\text{EtOH}} > 10^{-6} \text{ s}^{-1}$  (25°C).

The relative rate of formation of carbocations can be indicated inter alia with the aid of the ethanolysis constant  $k_{\text{EtOH}}$ , i.e. the rate constant for solvolysis in 100% ethanol at 25°C.

This determinant has been used in particular to indicate the relative reactivity of alkyl halides, especially of chlorides or bromides. The corresponding values for  $k_{\text{EtOH}}$  (25°C) can be taken from numerous publications (J.-P. Dau-Schmidt, H. Mayr, Chem. Ber. 1994, 127, 205-212; Dissertation J.-P. Dau-Schmidt, Medizinische Universität zu Lübeck 1992; P. Vogel, Carbocation Chemistry, Elsevier, Amsterdam, 1985, Chapter 7; G.A. Olah, P. von R. Schleyer, Carbonium Ions, Vol. 1-5, Interscience, New York, 1968-1976; X. Creary, Advances in Carbocation Chemistry, Vol. 1, JAI, Greenwich, CT, 1989; J.M. Coxon, Advances in Carbocation Chemistry, Vol. 2, JAI, Greenwich, CT, 1995). Further solvolysis rates can be determined by using the method described by Winstein and Grunwald (E. Grunwald, S. Winstein, J. Am. Chem. Soc. 1948, 70, 846-854; S. Winstein, E. Grunwald, H.W. Jones, J. Am. Chem. Soc. 1951, 73, 2700-2707).

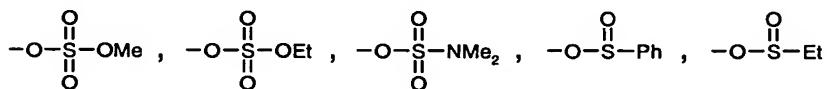
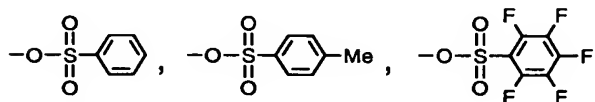
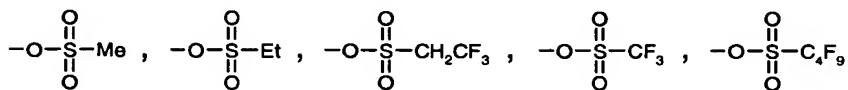
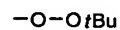
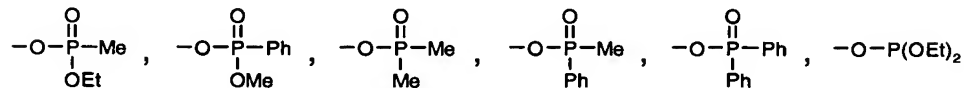
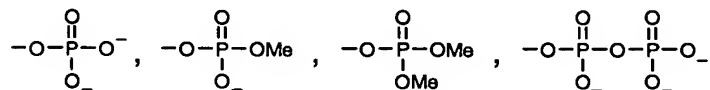
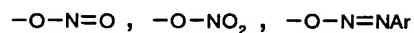
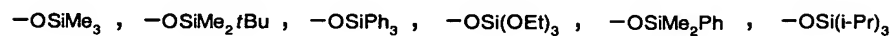
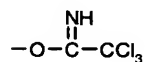
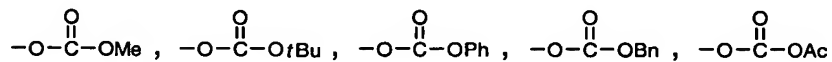
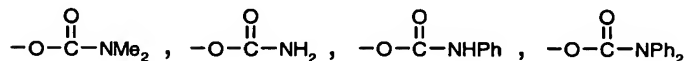
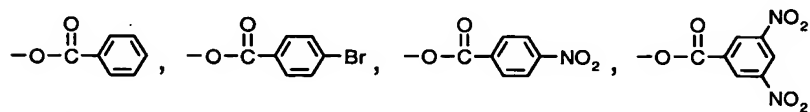
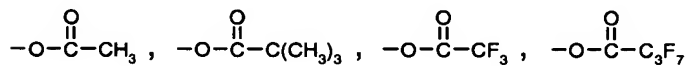
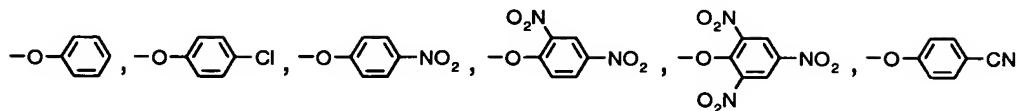
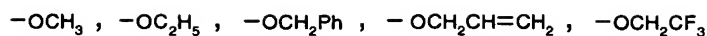
Examples of substituents  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  on the compounds of type (I) having the stated minimum values of  $k_{\text{EtOH}}$ , which do not, however, represent an exhaustive list, are substituents which are chosen independently of one another from the group of branched or unbranched alkyl, preferably  $\text{C}_1$ - $\text{C}_4$ -alkyl, in particular methyl, aryl, preferably  $\text{C}_6$ - $\text{C}_{10}$ -aryl, in particular phenyl, substituted aryl, heteroaryl which is unsubstituted or substituted preferably by amino, alkoxy or alkyl substituents, in particular 4-methoxyphenyl (anisyl) and 4-methylphenyl (tolyl), in particular thiophene, furan and pyrrole, branched or unbranched alkenyl, preferably  $\text{C}_2$ - $\text{C}_{10}$ -alkenyl, in particular 3-methylbut-2-enyl, cycloalk-2-enyl, preferably  $\text{C}_4$ - $\text{C}_7$ -cycloalk-2-enyl, in particular cyclopent-2-enyl and cyclohex-2-enyl, cyclo-, bicyclo- and tricycloalkyl, preferably  $\text{C}_3$ - $\text{C}_8$ -cycloalkyl and  $\text{C}_5$ - $\text{C}_8$ -bicyclo- and tricycloalkyl, alkoxy, preferably methoxy, ethoxy,

aryloxy or hydrogen. It is furthermore possible for two of the radicals  $R^1$ ,  $R^2$  and  $R^3$  to form an alkyl ring, preferably  $C_3$ - $C_8$ -cycloalkyl and  $C_5$ - $C_8$ -bicyclo- and tricycloalkyl.

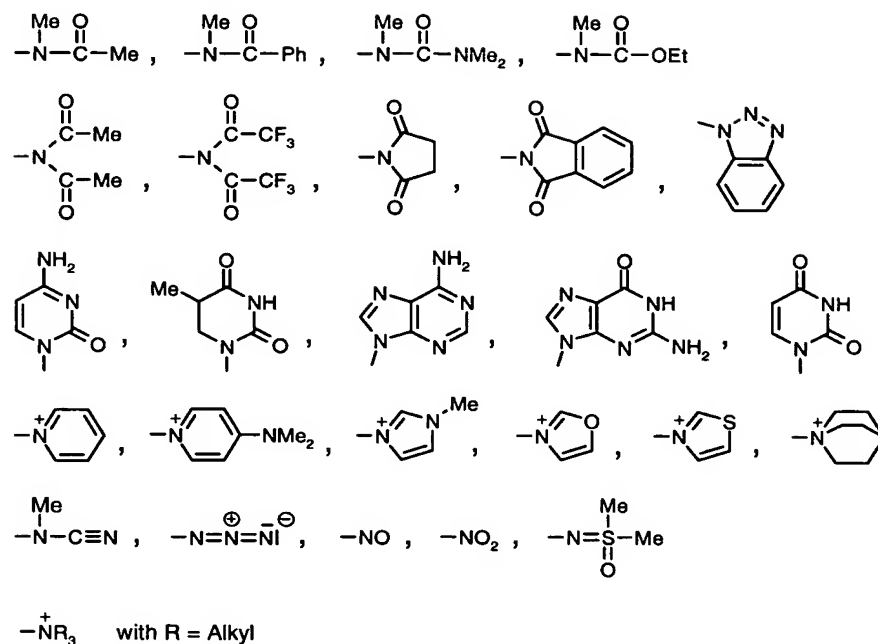
- X corresponds to a leaving group specified by the stated solvolysis rate; X is in particular halogen, alkoxy, preferably methoxy, ethoxy, and benzyloxy, alkyl- or arylsulphonato, in particular methanesulphonato, trifluoromethanesulphonato, benzenesulphonato, p-toluenesulphonato; however, it can also be chosen from the group of substituted or unsubstituted phenoxy, acyloxy, benzoyloxy, carbamoyl, alkyloxycarbonyloxy, aryloxycarbonyloxy, siloxy, in particular trimethylsiloxy, phosphato, phosphonato, hypophosphonato, alkylperoxy, sulphato, sulphenyl, sulphonyl, S-alkylsulphoxy, S-arylsulphoxy, alkylthio, arylthio, thiocyanato, isothiocyanato, ureato and imidyl. Compounds which have proved to be easily obtainable by synthesis and very effective are those with X = halogen. Halogen is fluorine, chlorine, bromine or iodine, preferably chlorine and bromine. A compilation of possible leaving groups is shown in list 1.1.

#### List 1.1

- 15 Halogen -I, -Br, -Cl, -F  
Oxygen substituents



## Nitrogen substituents



The  $\pi$  compounds which can be employed according to the invention as nucleophilic compounds in the method are aliphatic  $\pi$  nucleophiles such as, for example, substituted alkenes and alkynes, allyl- and propargylsilanes, alkyl enol ethers, silyl enol ethers, (silyl) ketene acetals and enamines, or aromatic  $\pi$  nucleophiles such as, for example, donor-substituted aromatic compounds, heteroaromatic compounds, preferably substituted or unsubstituted furans, thiophenes, pyrroles or indoles.

The  $\pi$  compounds employed are employed as solutions in a concentration range from 0.01 M to 20 M, preferably 0.1 M to 5 M, in particular 0.5 M to 2 M, in the solvents or solvent mixtures detailed below.

The solvents or solvent mixtures employed are or are composed of the group of alcohols, in particular ethanol, methanol, 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoroisopropanol, tetrahydrofuran, water, acetone, acetonitrile and dioxane.

In particular, acetone/water mixtures, preferably 80% aqueous acetone (80A20W (v/v)), acetonitrile/water mixtures, preferably 90% aqueous acetonitrile (90AN10W (v/v)), or pure 2,2,2-trifluoroethanol are used.

Solvolysis of compounds of type (I) in the solvents or solvent mixtures listed above follows the reaction scheme shown in Fig. 1, where SOH is the nucleophilic component in one of the solvents used:

Innumerable investigations into the rates and products of  $S_N1$  reactions have been carried out (J.-P. Dau-Schmidt, H. Mayr, Chem. Ber. 1994, 127, 205-212; Dissertation J.-P. Dau-Schmidt, Medizinische Universität zu Lübeck 1992; P. Vogel, Carbocation Chemistry, Elsevier, Amsterdam, 1985, Chapter 7; G.A. Olah, P. von R. Schleyer, Carbonium Ions, Vol. 1-5, Interscience, New York, 1968-1976; X. Creary, Advances in Carbocation Chemistry, Vol. 1, JAI, Greenwich, CT, 1989; J.M. Coxon, Advances in Carbocation Chemistry, Vol. 2, JAI, Greenwich, CT, 1995.). A considerable part of the knowledge about the relation between structure and reactivity of carbocations ( $R^1R^2R^3C^+$ ), the intermediates in these reactions, has been derived from solvolysis studies.

In the second reaction step of the reaction scheme shown in Fig. 1, the carbocation formed as intermediate is trapped by the appropriate solvent in a fast reaction.

The expert opinion is that such trapping reactions by solvents are too fast for a reaction to be possible between the carbocation generated as intermediate and any  $\pi$  nucleophile present.

Only in the specific example of the  $\alpha$ -(N,N-dimethylthiocarbamoyl)-4-methoxybenzyl cation has it been shown in mechanistic investigations that this intermediate can be trapped by  $\pi$  nucleophiles which are characterized by  $N > 6$  in the Mayr scale, when it is generated by solvolysis in 50% aqueous acetonitrile (50AN50W (v/v)). Since nucleophilicity parameters for solvents were not available at that time, this observation could not be generalized. It was neither evident that this must also apply to other types of carbocations, nor was it possible to derive consequences for organic synthesis. Since the Mayr publication (Angew. Chem. 1994, 106, 990-1010.) cited by Richard, the nucleophilicity parameters  $N$  and  $s$  have been published for many other  $\pi$  systems (H. Mayr, B. Kempf, A.R. Ofial, Acc. Chem. Res. 2003, 36, 66-77; B. Kempf, N. Hampel, A.R. Ofial, H. Mayr, Chem. Eur. J. 2003, 9, 2209-2218.). The values of  $N$  and  $s$  can be taken from these publications for many nucleophilic  $\pi$  systems.

The breakthrough to the present invention came about through the possibility of now determining, with the aid of photometric measurements by conventional UV-Vis spectroscopy, stopped flow methods and laser flash techniques, also N and s parameters for the solvents and solvent mixtures used according to the invention (Tab. 1).

5 **Tab. 1**

Solvent <sup>a</sup>	N	s
W	5.20	0.89
91W9AN	5.16	0.91
80W20AN	5.04	0.89
67W33AN	5.05	0.90
50W50AN	5.05	0.89
33W67AN	5.02	0.90
20W80AN	5.02	0.89
10W90AN	4.56	0.94
20W80A	5.77	0.87
10W90A	5.70	0.85
T	1.23	0.92
90T10W	2.93	0.88
80T20W	3.20	0.88
60T40W	3.42	0.90
50T50W	3.57	0.89
40T60W	3.77	0.88
20T80W	4.78	0.83
10T90W	5.04	0.90
E	7.44	0.90



Solvent <sup>a</sup>	N	s
90E10W	7.03	0.86
80E20W	6.68	0.85
60E40W	6.28	0.87
50E50W	5.96	0.89
40E60W	5.81	0.90
20E80W	5.54	0.94
10E90W	5.38	0.91
91E9AN	7.10	0.90
80E20AN	6.94	0.90
67E33AN	6.74	0.89
50E50AN	6.37	0.90
33E67AN	6.06	0.90
20E80AN	5.77	0.92
10E90AN	5.19	0.96
M	7.54	0.92
91M9AN	7.45	0.87
80M20AN	7.20	0.89
67M33AN	7.01	0.91
50M50AN	6.67	0.90
33M67AN	6.38	0.92
20M80AN	6.04	0.94
10M90AN	5.55	0.97

<sup>a</sup> Solvent mixtures are indicated in % by volume (v/v): M = methanol, E = ethanol, W = water, T = 2,2,2-trifluoroethanol, AN = acetonitrile, A = acetone. The number preceding the respective abbreviation for the solvent corresponds to the statement of amount in %.

In addition, approximate values for many further solvents and solvent mixtures have been determined by correlating the  $N$  values obtained by the Mayr research group with the nucleophilicity values  $N_T$  determined by the Kevill research group (Advances in Quantitative Structure-Property Relationships, Vol. 1, Charton, M. ed., JAI Press, 5 Greenwich, Connecticut, 1996, 81-115) from rates of solvolysis of methylsulphonium ions (Table 2).

**Tab. 2**

a	$N_T^b$	$N^c$
70E30W	-0.20	6.48 <sup>d</sup>
30E70W	-0.93	5.68 <sup>d</sup>
95A5W	-0.49	6.05
70A30W	-0.42	6.16
60A40W	-0.52	6.00
50A50W	-0.70	5.73
40A60W	-0.83	5.54
30A70W	-0.96	5.34
20A80W	-1.11	5.11
10A90W	-1.23	4.93
80D20W	-0.46	6.10
70D30W	-0.37	6.23
60D40W	-0.54	5.97
50D50W	-0.66	5.79
40D60W	-0.84	5.52
20D80W	-1.12	5.10
97T3W <sup>e</sup>	-3.30	1.81
80T20W <sup>e</sup>	-2.19	3.48
80T20E	-1.76	4.13
60T40E	-0.94	5.37

a	$N_T^b$	$N^c$
50T50E	-0.64	5.82
40T60E	-0.34	6.28
20T80E	0.08	6.91
97H3W <sup>e</sup>	-5.26	-1.15
90H10W <sup>e</sup>	-3.84	0.99
70H30W <sup>e</sup>	-2.94	2.35
50H50W <sup>e</sup>	-2.49	3.03

<sup>a</sup> Solvent mixtures are indicated in % by volume (v/v): M = methanol, E = ethanol, W = water, T = 2,2,2-trifluoroethanol, A = acetone, D = dioxane, H = 1,1,1,3,3,3-hexafluoro-2-propanol.

5 <sup>b</sup> Kevill  $N_T$  values. <sup>c</sup> A typical  $s$  parameter of 0.9 is proposed for these solvents (mixtures).

<sup>d</sup> Interpolated value. <sup>e</sup> Solvent (mixtures) in % by weight.

10 It is now possible with these newly determined parameters to compare the nucleophilicity of the solvents and solvent mixtures employed according to the invention with the nucleophilicity of typical  $\pi$  systems (cf. Fig. 2).

Comparison of the nucleophilicity parameters  $N$  for solvents (mixtures) with  $N$  parameters of typical  $\pi$  systems; solvent mixtures are indicated in % by volume (v/v): M = methanol, E = ethanol, W = water, T = 2,2,2-trifluoroethanol, AN = acetonitrile, H = 1,1,1,3,3,3-hexafluoro-2-propanol (further solvents can be taken from Tables 1 and 2).

15 If the  $\pi$  system in question is above the respective solvent in Fig. 2, it is able to trap a carbocation generated in this solvent. Since the  $N$  parameters of  $\pi$  systems are changed somewhat by solvent effects it is also possible for  $\pi$  systems which are up to two units below the respective solvent in Fig. 2 to trap the intermediate carbocations.

20 It is more preferred to employ in the claimed method solutions of  $\pi$  systems whose  $N$  parameter is greater than that of the solvent or solvent mixture used in each case.

The addition of the electrophiles of the general formula (I) was possibly preceded by also adding to the solutions basic supplements which trap the resulting acids HX (X is

preferably halogen, in particular chlorine or bromine) resulting as by products in the reactions.

- 5 Supplements employed were basic inorganic and organic compounds, preferably bicarbonates, carbonates and pyridines, especially ammonium bicarbonate ( $\text{NH}_4\text{HCO}_3$ ), sodium bicarbonate ( $\text{NaHCO}_3$ ), ammonium carbonate [ $(\text{NH}_4)_2\text{CO}_3$ ], 2-chloropyridine and 2,6-lutidine. The choice of the supplement was determined by comparative experiments in the particular case.

- 10 The reaction times are generally from 1 second to 2 days, preferably 1 minute to 5 hours.

The progress of the reaction can be followed for example with GCMS or NMR spectroscopic investigations.

All the isolated products were characterized unambiguously by NMR spectroscopy methods, GCMS, IR and, in some cases, elemental analyses.

- 15 General procedure for carrying out the syntheses:

- The electrophile is added to a solution of the  $\pi$  compound in the solvent or solvent mixture indicated in each case, preferably a 0.5 to 2 molar solution of the nucleophile (which is preferably employed in 1.1 to 10 equivalents relative to the electrophile), and possible addition of, preferably, 1 to 3 equivalents (eq) (relative to the electrophile employed) of the basic supplement, sufficiently slowly for the heat of reaction to be dissipated without problem. In the case of solids, these are either added in portions or dissolved in the minimum amount of inert solvent, such as acetonitrile, and added dropwise. The reaction mixture is preferably stirred according to the invention at room temperature (rt).

- 25 After the reaction is complete the same volume of water is added to the reaction mixture, and the aqueous phase is extracted several times with diethyl ether. The combined organic extracts are dried over a desiccant, preferably sodium sulphate or magnesium sulphate, and excess solvent is removed in vacuo.

The residues are subjected to further purification, for example a distillation or a chromatography on silica gel.

The syntheses can be carried out on a larger scale maintaining the stoichiometry of the substances employed.

## 5 **Examples**

General procedure for carrying out the syntheses:

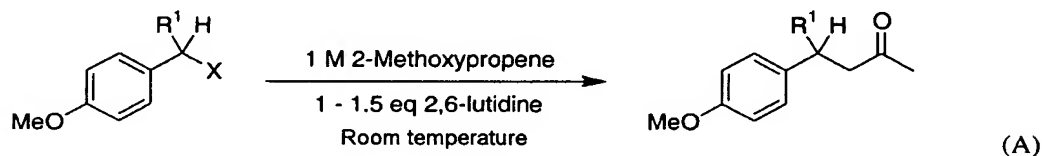
The electrophile is added to a solution of the  $\pi$  compound in the solvent or solvent mixture indicated in each case, preferably a 0.5 to 2 molar solution of the nucleophile (which is preferably employed in 1.1 to 10 equivalents relative to the electrophile), and possible addition of, preferably, 1 to 3 equivalents (eq) (relative to the electrophile employed) of the basic supplement, sufficiently slowly for the heat of reaction to be dissipated without problem. In the case of solids, these are either added in portions or dissolved in the minimum amount of inert solvent, such as acetonitrile, and added dropwise. The reaction mixture is preferably stirred according to the invention at room temperature (rt).

After the reaction is complete the same volume of water is added to the reaction mixture, and the aqueous phase is extracted several times with diethyl ether. The combined organic extracts are dried over a desiccant, preferably sodium sulphate or magnesium sulphate, and excess solvent is removed in vacuo.

The residues are subjected to further purification, for example a distillation or a chromatography on silica gel.

**Examples 1 – 2**

By the claimed method, following the general procedure, various electrophiles were reacted with 2-methoxypropene ( $N = 5.41$ ,  $s = 0.91$ ) in analogy to the following reaction scheme (A). The employed solvents (mixtures), bases, reaction conditions and yields are to be found in Tab. 3.

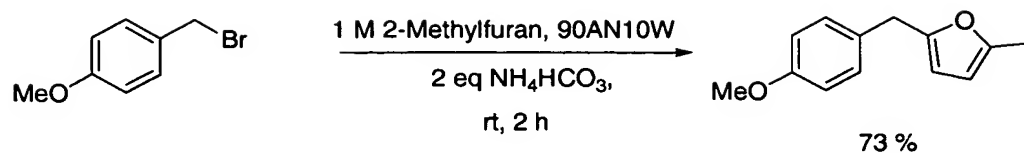


No.	R <sup>1</sup>	X	n <sub>El</sub> [mmol]	n <sub>Nu</sub> [mmol]	t [min]	Solvent	V <sub>Solv+Nu</sub> [ml]	Base	Yield
1	4-Methoxy-phenyl	Cl	3.81	25	15	90AN10W	25	2,6-Lutidine	62 %
2	H	Br	4.97	25	180	90AN10W	25	2,6-Lutidine	67 %

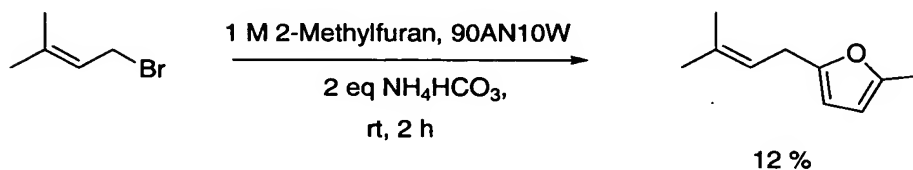
Tab. 3 -  $n_{El}$  = amount of substance of electrophile,  $n_{Nu}$  = amount of substance of nucleophile,  $V_{Solv+Nu}$  = total volume of the 1 molar solution of the nucleophile.

**Example 3 – 7**

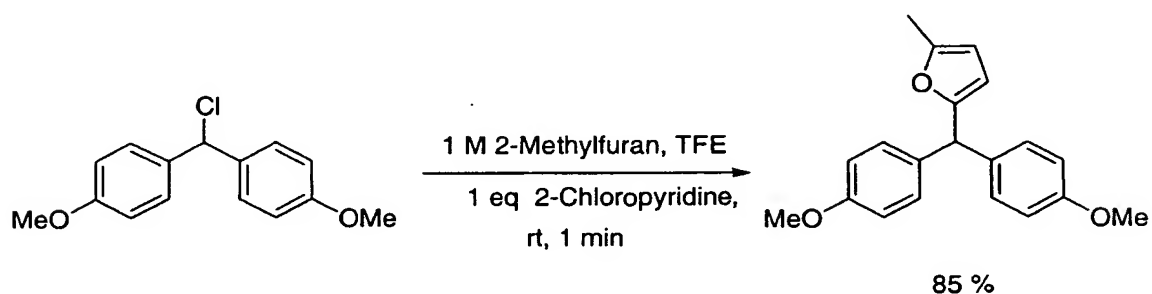
- 10 By the claimed method, various electrophiles were reacted with 2-methylfuran ( $N = 3.61$ ,  $s = 1.11$ ) in the stated solvents (mixtures) in accordance with the general procedure at room temperature (rt). The respectively employed solvents (mixtures), bases (eq relative to the electrophile), nucleophile concentrations and yields are to be found in the reaction equations.
- 15 Reaction of 4-methoxybenzyl bromide (4.97 mmol) with a 1 molar solution (25 ml) of 2-methylfuran (25 mmol) in 90% aqueous acetonitrile (Example 3):



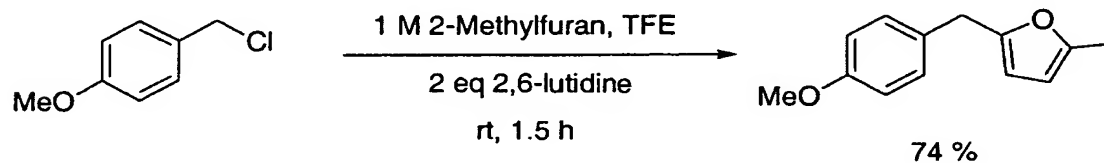
Reaction of prenyl bromide (6.71 mmol) with a 1 molar solution (20 ml) of 2-methylfuran (20 mmol) in 90% aqueous acetonitrile (Example 4):



- 5 Reaction of chlorobis(4-methoxyphenyl)methane (3.81 mmol) with a 1 molar solution (20 ml) of 2-methylfuran (20 mmol) in 2,2,2-trifluoroethanol (Example 5):

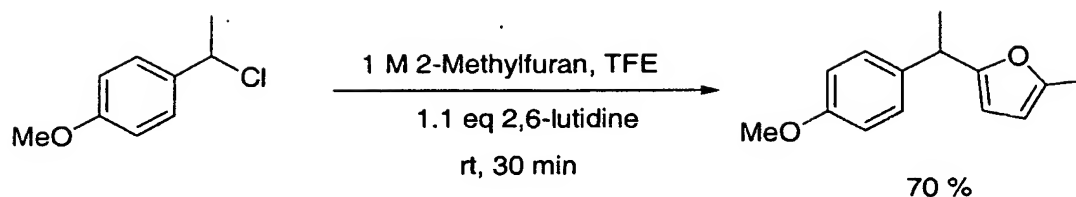


Reaction of 4-methoxybenzyl chloride (12.8 mmol) with a 1 molar solution (50 ml) of 2-methylfuran (50 mmol) in 2,2,2-trifluoroethanol (Example 6):

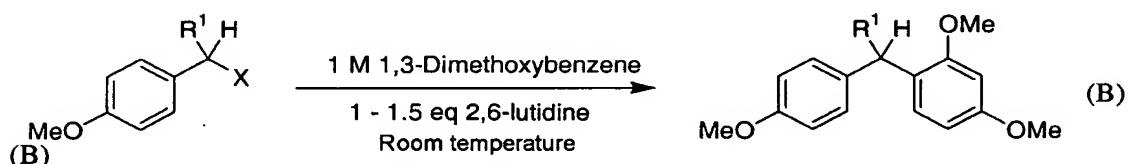


10

Reaction of 1-anisylethyl chloride (5.86 mmol) with a 1 molar solution (25 ml) of 2-methylfuran (25 mmol) in 2,2,2-trifluoroethanol (Example 7):

**Examples 8 – 10**

By the claimed method, following the general procedure various electrophiles were reacted with 1,3-dimethoxybenzene ( $N = 2.48$ ;  $s = 1.09$ ) in 2,2,2-trifluoroethanol (TFE) in analogy to the following reaction scheme (B). The employed bases, reaction conditions and yields are to be found in Tab. 4.



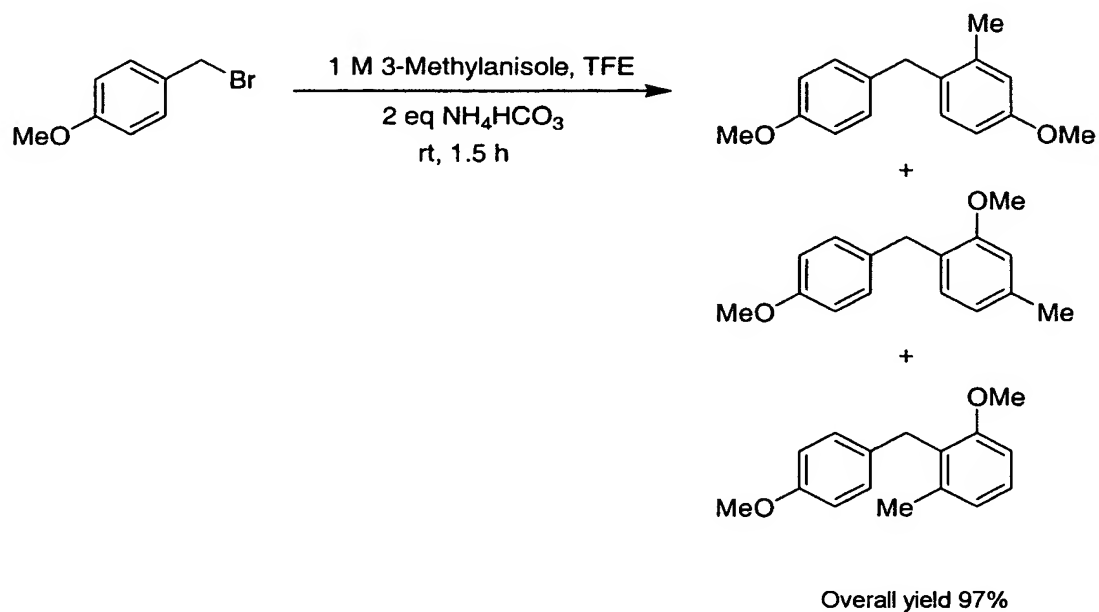
No.	R <sup>1</sup>	X	n <sub>El</sub> [mmol]	n <sub>Nu</sub> [mmol]	V <sub>Solv+Nu</sub> [ml]	t [min]	Base	Yield
8	H	Cl	6.39	25	25	30	1.5 eq 2,6-Lutidine	84 % + 7 % 1,2,3-substitution
9	H	Cl	6.39	25	25	30	---	79 % + 5 % 1,2,3-substitution
10	Me	Cl	5.86	25	25	30	1.1 eq 2,6-Lutidine	52 %

Tab. 4 -  $n_{El}$  = amount of substance of electrophile,  $n_{Nu}$  = amount of substance of nucleophile,  $V_{Solv+Nu}$  = total volume of the 1 molar solution of the nucleophile.



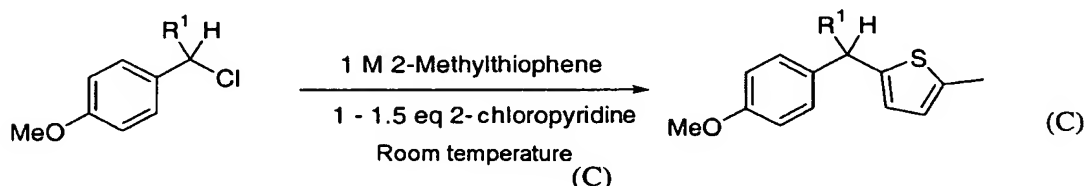
**Example 11**

By the claimed method, following the general procedure 4-methoxybenzyl bromide (3.73 mmol) was reacted with a 1 molar solution (25 ml) of 3-methylanisole (N = 0.13; s = 1.27) (25 mmol) in 2,2,2-trifluoroethanol (TFE) in analogy to the following reaction scheme. The employed base, the reaction conditions and the yield are evident from the reaction equation.



**Examples 12 – 13**

By the claimed method, following the general procedure various electrophiles were reacted with 2-methylthiophene ( $N = 1.26$ ;  $s = 0.96$ ) in 2,2,2-trifluoroethanol (TFE) in analogy to the following reaction scheme (C). The employed bases, reaction conditions and yields are to be found in Tab. 5.



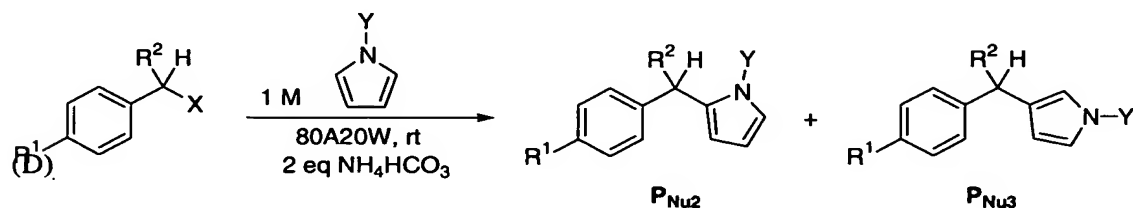
No.	R <sup>1</sup>	X	n <sub>El</sub> [mmol]	n <sub>Nu</sub> [mmol]	V <sub>Solv+N<sub>u</sub></sub> [ml]	t [min]	Base	Yield
12	4-Methoxy-phenyl	Cl	3.81	20	20	2	1.1 eq 2-Chloropyridine	83 %
13	Me	Cl	5.86	25	25	30	1.1 eq 2-Chloropyridine	81 %

Tab. 5 -  $n_{El}$  = amount of substance of electrophile,  $n_{Nu}$  = amount of substance of nucleophile,  $V_{Solv+N<sub>u</sub>}$  = total volume of the 1 molar solution of the nucleophile.

10 **Examples 14 – 17**

By the claimed method, following the general procedure various electrophiles were reacted with 1-methylpyrrole ( $N = 5.85$ ;  $s = 1.03$ ) and pyrrole ( $N = 4.63$ ;  $s = 1.00$ ) in 80% aqueous acetone (80A20W) or water (W) in analogy to the following reaction scheme (D). The solvent used in each case, the reaction conditions and yields are to be found in

15 Tab. 6.

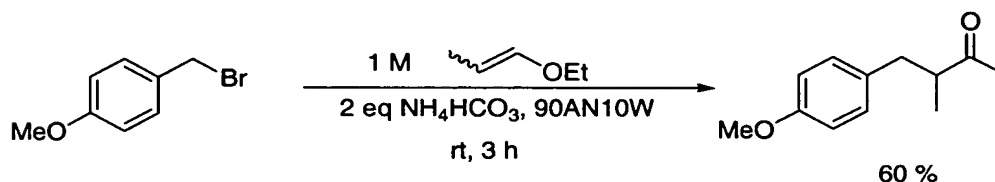


No.	R <sup>1</sup>	R <sup>2</sup>	X	Y	Solvent	n <sub>EI</sub> [mmol]	n <sub>Nu</sub> [mmol]	V <sub>Solv+N<sub>u</sub></sub> [ml]	t [h]	Yield P <sub>Nu2</sub> /P <sub>Nu3</sub>
14	OMe	H	Br	Me	80A20W	4.97	25	25	0.5	49 % / 21 %
15	H	Ph	Cl	Me	80A20W	4.93	25	25	24	47 % / 21 %
16	H	Ph	Br	H	80A20W	4.05	25	25	0.5	81 % / 13 %
17	H	Ph	Br	H	W	6.25	25	25	0.5	74 % / 2 %

Tab. 6 - n<sub>EI</sub> = amount of substance of electrophile, n<sub>Nu</sub> = amount of substance of nucleophile, V<sub>Solv+N<sub>u</sub></sub> = total volume of the 1 molar solution of the nucleophile.

### Example 18

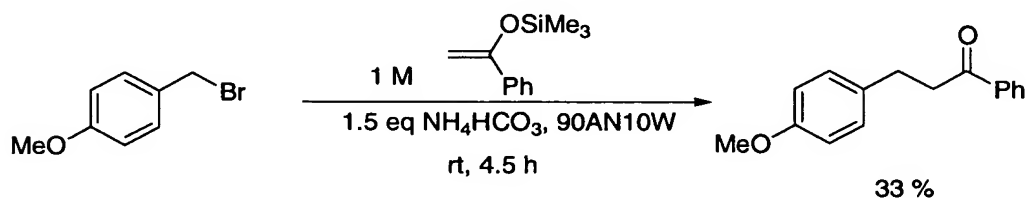
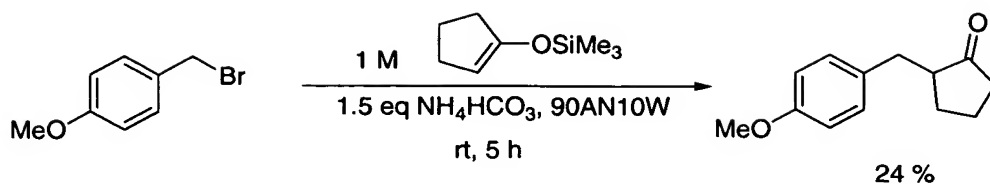
By the claimed method, following the general procedure 4-methoxybenzyl bromide (2.49 mmol) was reacted with a 1 molar solution (25 ml) of ethyl prop-1-enyl ether (cis/trans isomer mixture) (25 mmol) in 90% aqueous acetonitrile (90AN10W) in analogy to the following reaction scheme. The base employed, the exact reaction conditions and the yield are indicated in the reaction equation.



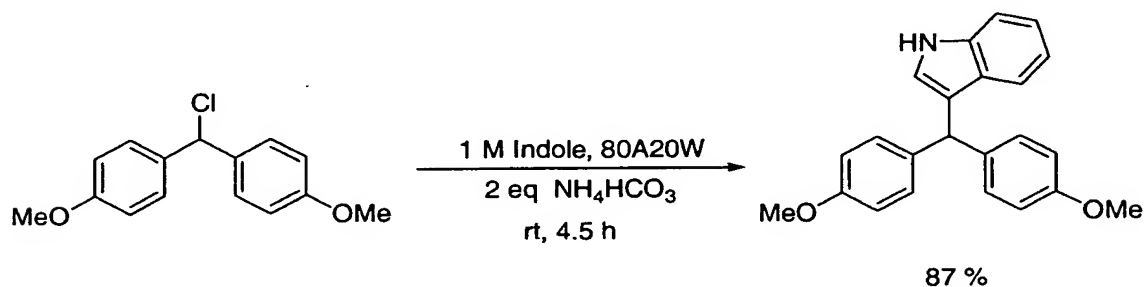
### Examples 19 – 20

By the claimed method, following the general procedure 4-methoxybenzyl bromide was reacted with 1-trimethylsiloxycyclopentene (N = 6.57; s = 0.93) and 1-phenyl-1-trimethylsiloxyethylene (N = 6.22; s = 0.96) in 90% aqueous acetonitrile (90AN10W) in analogy to the following reaction schemes. The employed bases, reaction conditions and yields are indicated in the respective reaction equation.

Reaction of 4-methoxybenzyl bromide (1.24 mmol) with a 1 molar solution (10 ml) of 1-trimethylsiloxycyclopentene (10 mmol) in 90% aqueous acetonitrile (90AN10W) (Example 19):

**Example 21**

By the claimed method, following the general procedure chlorobis(4-methoxyphenyl)methane (3.81 mmol) was reacted with a 1 molar solution (25 ml) of indole ( $N = 5.80$ ;  $s = 0.80$ ) (25 mmol) in 80% aqueous acetone (80A20W) in analogy to the following reaction scheme. The employed base, reaction conditions and the yield are

**Examples 22 – 46:**

The reactions shown in Tab. 7 were carried out by the claimed method and following the general procedure. Nucleophiles, electrophiles and the amounts of substance n thereof employed, solvents (solvent mixtures) and the volumes V thereof, bases employed where appropriate, and the equivalents thereof relative to the amount of substance of the

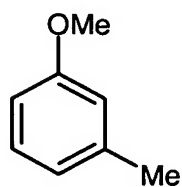
electrophile, reaction time  $t$  and the yields are to be found in Tab. 7. The reactions were carried out at room temperature, unless stated otherwise.

Tab. 7:

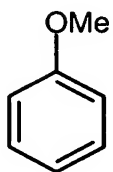
No.	Nucleophile <sup>[a]</sup>	n [mmol]	Electrophile <sup>[b]</sup>	n [mmol]	Solvent <sup>[c]</sup>	V [ml]	Base (eq. relative to electrophile)	Yield [%] <sup>[d]</sup>	t
22	3-Methylanisole	25	Ani <sub>2</sub> CHCl	5.00	TFE	25	2-Chloropyridine (1.5)	96	1 h
23	Anisole	23.8	(3-Cl)(3'-Cl)CHCl	2.15	TFE	10	NH <sub>4</sub> HCO <sub>3</sub> (2.3)	30	24 h
24	Anisole	9.2	(3-Cl)PhCHCl	0.11	TFE	5	NH <sub>4</sub> HCO <sub>3</sub> (1.8)	36	1 h
25	Anisole	23.8	(Ani)PhCHCl	2.00	TFE	10	NH <sub>4</sub> HCO <sub>3</sub> (2.5)	88	2 h
26	Anisole	23.8	(Ani)PhCHCl	2.00	TFE	10	2-Chloropyridine (1.2)	86	3 d
27	Anisole	23.8	Ani <sub>2</sub> CHCl	2.99	TFE	25	NH <sub>4</sub> HCO <sub>3</sub> (1.7)	70	30 min
28	Anisole	23.8	Ani <sub>2</sub> CHCl	2.99	TFE	25	2-Chloropyridine (1.2)	88	3 h
29	Anisole	10	Ph <sub>2</sub> CHBr	3.33	H	10	NH <sub>4</sub> HCO <sub>3</sub> (1.5)	80	1 h
30	Anisole	25	Ph <sub>2</sub> CHCl	3.04	TFE	25	NH <sub>4</sub> HCO <sub>3</sub> (1.7)	94	1 h
31	Anisole	25	Ph <sub>2</sub> CHCl	3.04	TFE	25	2-Chloropyridine (1.2)	84	1 d
32	Anisole	23.8	p-OMe- $\alpha$ -MeBnCl	2.43	TFE	5	NH <sub>4</sub> HCO <sub>3</sub> (2.1)	66	30 min
33	Anisole	23.8	p-OMe- $\alpha$ -MeBnCl	2.43	TFE	5	2-Chloropyridine (1.2)	64	6 h
34	Anisole	23.8	Tol <sub>2</sub> CHCl	3.02	TFE	25	NH <sub>4</sub> HCO <sub>3</sub> (1.7)	96	3 h
35	Anisole	23.8	Tol <sub>2</sub> CHCl	3.02	TFE	25	2-Chloropyridine (1.2)	90	1 d
36	Dimethylaniline	10	Ani <sub>2</sub> CHCl	3.33	90AN10W	10	NH <sub>4</sub> HCO <sub>3</sub> (1.5)	86	1 d
37	Dimethylaniline	10	Ph <sub>2</sub> CHBr	3.33	90AN10W	10	NH <sub>4</sub> HCO <sub>3</sub> (1.5)	73	20 h
38	Dimethylaniline	10	p-OMeBnBr	3.33	100AN	10	---	69	3 h <sup>[e]</sup>

No.	Nucleophile <sup>[a]</sup>	n [mmol]	Electrophile <sup>[b]</sup>	n [mmol]	Solvent <sup>[c]</sup>	V [ml]	Base (eq. relative to electrophile)	Yield [%] <sup>[d]</sup>	t
39	Dimethylaniline	10	p-OMeBnBr	3.33	100AN	10	NH <sub>4</sub> HCO <sub>3</sub> (1.5)	82	2 h <sup>[e]</sup>
40	Dimethylaniline	10	p-OMeBnBr	3.33	90AN10W	10	NH <sub>4</sub> HCO <sub>3</sub> (1.5)	86	1.5 h <sup>[e]</sup>
41	Mesitylene	10	Ph <sub>2</sub> CHBr	3.33	H	10	NH <sub>4</sub> HCO <sub>3</sub> (1.5)	74	2 h
42	N-Methylindole	25	p-OMeBnBr	5.00	80A20W	25	NH <sub>4</sub> HCO <sub>3</sub> (2)	73	1 h
43	N-Methylpyrrole	20.23	Ph <sub>2</sub> CHBr	4.05	-	-	-	71	1 d
44	Pyrrole	20.23	Ph <sub>2</sub> CHBr	4.05	-	-	-	48	2 h
45	Pyrrole	25	Ph <sub>2</sub> CHBr	8.33	W	25	NH <sub>4</sub> HCO <sub>3</sub> (2)	62	1 h
46	Pyrrole	10	Tol <sub>2</sub> CHCl	3.33	80A20W	10	NH <sub>4</sub> HCO <sub>3</sub> (2)	90	1 h

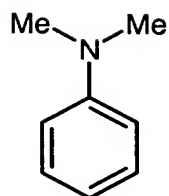
[a] Annexed figures formula *annexed* – nucleophiles. [b] Annexed figures formula *annexed* – electrophiles. [c] Solvent mixtures are indicated in % by volume, the meanings being: W = water, TFE = 2,2,2-trifluoroethanol, H = 1,1,1,3,3,3-hexafluoroisopropanol, AN = acetonitrile, A = acetone. [d] isolated material, [e] reaction temperature 85°C.

**Formula annex - nucleophiles in Tab. 7**

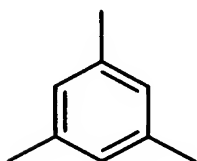
3-Methylanisole



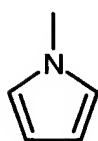
Anisole



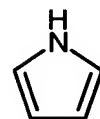
Dimethylaniline



Mesitylene

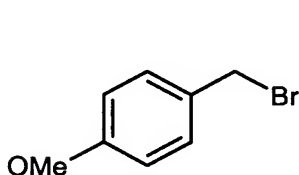


N-Methylpyrrole

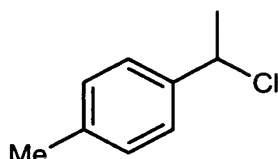


Pyrrole

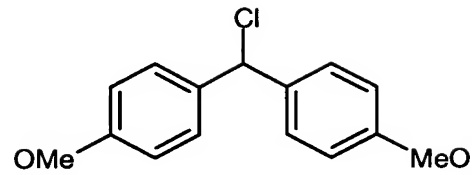
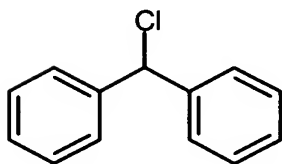
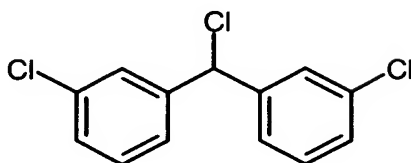
5

**Formula annex – electrophiles in Tab. 7**

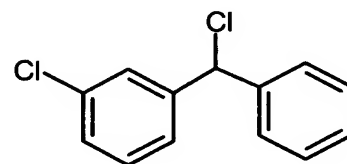
p-OMeBnBr



p-OMe-α-MeBnCl

Ani<sub>2</sub>CHClPh<sub>2</sub>CHCl

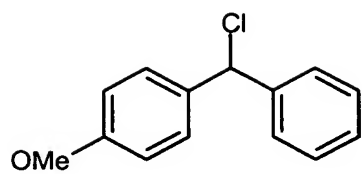
(3-Cl)(3'-Cl)CHCl



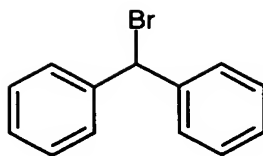
(3-Cl)PhCHCl

10

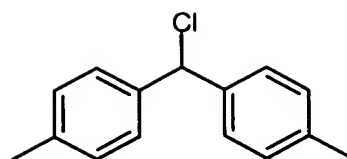




(Ani)PhCHCl



PhCH<sub>2</sub>Br



Tol<sub>2</sub>CHCl